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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/783,487 | 02/14/2001 | Tito Andrew Serafini | 10239-010 | 7095 |

20583 7590 09/24/2003

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| EXAMINER |
|---|
| WOITACH, JOSEPH T |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | 16 |

DATE MAILED: 09/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/783,487 | SERAFINI, TITO ANDREW | |
| | Examiner | Art Unit | |
| | Joseph T. Woitach | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *30 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-27 and 32-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-27 and 32-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9, 13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

This is an original application, filed February 14, 2001.

Applicants' amendment filed June 30, 2003, paper number 15, has been received and entered. The specification has been amended. Claims 28-31 and 61-158 have been canceled. Claims 1-27 and 32-60 are pending and currently under examination.

### *Information Disclosure Statement*

The information disclosure statement filed July 23, 2002, paper number 9, did not include a copy of each of the references listed. Applicants have supplied a copy of the references listed therein. Additionally, a supplemental information disclosure has been submitted April 2, 2003, paper number 13. Copies of the signed IDS forms are included with this action.

### *Specification*

The disclosure objected to because it contained embedded hyperlink and/or other form of browser-executable code is withdrawn.

The amendments to the specification has obviated the basis of the objection.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-27 and 32-60 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants summarize the basis of the rejection (page 29 and at the start of relevant subsections) and summarize the standards set forth in the courts for establishing what is considered 'undue experimentation' (page 29). With respect to providing promoters for characterizing genes Applicants point to the teachings of the specification which set forth the invention as it pertains to the expression pattern and portions which would define what would be functionally required in identifying sequences that meet the functional limitations. More specifically, the specification teaches that large genomic sequences can be obtained in YAC and BAC vectors and that many genomic and regulatory sequences therein can be easily obtained because they are already publicly available. Given the teachings of the specification and the information known in the art Applicants argue that the skilled artisan would be able to obtain large regulatory sequences of a gene and test such sequences to obtain regulatory sequences which required by the limitations set forth in claims. Additionally, Applicants argue that the office has not met its initial burden for establishing why one would not be able to obtain specific genes and subsequently their regulatory sequences which affect specific pathways and affect

specific phenotypes when expressed in a transgenic animal. See pages 29-33, subsection 1.

With respect to specific rejections regarding enabling the specific expression pattern of a heterologous transgene, Applicants note the teachings of the references provided and argue the references support Applicants invention indicating that the problems associated with obtaining specific expression patterns can be remedied by further optimization of the regulatory sequences. as argued above, Applicants note that sequences which are larger than those disclosed can be obtained until such sequences are optimized to provide the expression pattern required by the claimed invention. See pages 34-37, subsection 2.

With respect to the unpredictability of transgene expression Applicants note the cited references and argue that unlike the present invention the examples are directed to transgene expression which using heterologous promoters not regulatory of endogenous genes. Applicants argue that any aberrant expression with regard to "Viability and phenotypic issues may, in general, be overcome with routine experimentation" (page 38). Further, Applicants argue that IRES sequences are known and one can adapt the use of IRES with routine experimentation to meet the functional limitations encompassed by the claims. See pages 37-43, subsection 3. See Applicants' amendment, pages 28-40, Section B. Applicants' arguments have been fully considered, but not found persuasive.

Initially, it is noted that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman*, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991). Further, Examiner

acknowledges and agrees that "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation." However, " The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Examiner agrees with the summary of the basis of the rejection set forth by Applicants and notes that in response to each of the specific basis of the rejection Applicants argue and rely on the skilled artisan for optimizing sequences to obtain and practice the claimed method. These arguments are not found persuasive because each specific basis of the rejection is an art recognized limitation. Examiner has provided sound scientific reasoning and specific scientific references supporting the basis of the rejection, thus providing a *prima facie* case. The particular teachings in the specification are noted, however none of the general guidance provides the necessary guidance to overcome art recognized limitations set forth in the basis of the rejection. Applicants' arguments do not contest the art recognized limitations set forth in the basis of the rejection, rather the traverse of the rejection focuses primarily on the skilled artisan overcoming these limitations through routine optimization. Further, it is noted that Applicants arguments asserting that it would require routine experimentation are not specifically supported by any of the references of record, in particular as they pertain to providing predictable expression in the context of a transgenic animal. Examiner would agree that promoter analysis in cells *in vitro* is common and routine, however even *in vitro* expression pattern of a regulatory sequence is not predictable and is subject to position of the transgene insertion into the genome, type of cell, nature of the promoter

and other unknown factors affected by the conditions of the cell. More importantly, even when provided with a detailed expression pattern of the endogenous gene and a characterization of the 'isolated' promoter, the expression pattern would not simply extend to its use in a transgenic animal for providing the same expected expression pattern *in vivo*. The art recognizes that expression of a heterologous transgene in transgenic animals is subject to many variables without any clear expectation of successfully meeting the limitations set forth and encompassed by the instant claims. Moreover, because characterization and optimization of promoter activity *in vitro* does not simply extend the use of promoter sequences in transgenics *in vivo*, any optimization for use of specific sequences would have to be done *in vivo*. As noted in the previous office action, while Examiner would agree that the methodology for inserting a transgene into a the genome of an animal are becoming common, any methodology for optimizing promoters in this context is not routine. Further, given the unpredictability of transgene expression, even if sufficient materials and facilities could be provided to carry out the experiments for optimization, there is no simple expectation of success that a transgene in particular a promoter sequence out of the physical context of the endogenous gene would provide the same expression pattern as the endogenous gene. Examiner acknowledges that the specification has reduced to practice a large BAC genomic sequence and made modifications to said sequence, however there is no evidence that in the context of a transgenic animal that the sequences would meet the limitations for the required expression pattern set forth in the claims. The examples provided in the instant specification fail to demonstrate that such methodology overcomes art recognized limitations for

transgene expression. With respect to dependent claims reciting specific pathways (for example claim 17) and encompassing providing yet undefined genes in the context of specific disease states (claim 21), there is no evidence that art recognized limitation would not apply to these subsets of genes as well. It is also important to note that the specific diseases recited by the claims are complex and not all associated with any particular gene or gene expression. The amount of work in identifying, characterizing and establishing the correlation of a single gene to a particular disease is the subject of skilled artisans entire work. In addition to arguments provided above, the amount of experimentation to practice even the specific limitations set forth in dependent claims would be considered require more than experimentation. In this case, the identification of a specific genotype or phenotype cannot be considered a minor detail which can be omitted in the process of providing an enabling disclosure.

Enablement has been considered in view of the Wands factors (MPEP 2164.01(a)). In view of the quantity of experimentation required, the limited amount and general guidance presented, the absence of working examples supporting the claimed invention, the nature and breadth of the claimed invention, the state of the prior art and unpredictability of the art, it would have required undue experimentation to make and/or use the invention as claimed. Therefore, for the reasons above and of record, the rejection is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-27 and 32-60 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With respect to claims 1 and 32 Applicants point to the specification starting at page 13, line 33 noting the "substantially the same expression pattern" is specifically defined and argue that the patentee can be his own lexicographer and that the metes and bounds of the claims are clear in light of Applicants definition. See Applicants' amendment, pages 40-41, Section C. Applicants arguments have been fully considered, but not found persuasive.

Examiner notes the definition of "substantially the same expression pattern" provided in the instant disclosure and acknowledges that Applicants can be their own lexicographer to provide definitions to particular terms used. However, the definition provided is insufficient to clearly define the metes and bounds of the term and hence the claims. The definition indicates the percentages of cells in which one wishes the transgene to be expressed as compared to the normal endogenous expression pattern, however it fails to clearly indicate is other cells not normally expression the endogenous gene may also express the transgene. For example, it is not clear if a transgenic animal in which all the cells of the animal express the transgene under a more promiscuous promoter would anticipate the claims because clearly it would meet the limitation of expression of even "100% of the cells shown to express the endogenous characterizing gene by *in situ* hybridization". Further, this definition in part implies that expression of the endogenous gene must be detectable by *in situ* hybridization and it is unclear if

claims where the transgene expression pattern is present in 100% of the cells normally expressing the endogenous gene but can not be detected by in situ hybridization or would anticipate the claims. Finally, the definition provides no context to what is encompassed by the term "pattern" in particular with respect to any aspect of regulated expression times or levels of expression in the cell(s). Examiner acknowledges the definition provided in the specification however as set forth above and the previous office action, the recitation of "substantially the same expression pattern" as supported by the present specification is indefinite because it fails to clearly define the metes and bonds and types of expression patterns that are encompassed by the claims. The artisan can not clearly identify what would be excluded or include because the term and definition fails clearly define necessary elements of the 'expression pattern' encompassed by the claim.

With respect to claims 7 and 38, Applicants reiterate that the limitation of claims 7 and 38 within the respective context of independent claims 1 and 32 and argue that the claims are clear and definite. See Applicants' amendment, top of page 41. Applicants' arguments have been fully considered, but not found persuasive.

It is maintained that the functional relationship of the IRES to the other sequences is not clearly set forth. Within the scope of the claims and in the context of the invention the 'characterizing gene' could be either the endogenous gene or the transgene. Further, there is no specific context set forth in the claims for the heterologous sequences in the genome. It is unclear if claims 7 and 38 are provided to simply exclude knock-out animal made with gene trap

vectors or with constructs which allow for both the endogenous gene and a transgene marker to be expressed from the endogenous promoter, and that claim 1 would be anticipated by a the commercially available knock-out animals meeting the functional limitations of the claim.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> a person shall be entitled to a patent unless -
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 14, 18, 19, 22, 32, 33, 45, 49, 50, 53, 56 and 60 stand rejected under 35 U.S.C. 102(e) as being anticipated by Leinwand *et al.* (US Patent 6,353,151).

Applicants summarize the claims and specific embodiments required to be encompassed by the instant claims and argue that Leinwand *et al.* only teaches the use of regulatory sequences of a single gene of a heart specific promoter, and fails to disclose regulatory sequences from different characterizing genes. See Applicants amendment, pages 41-42, Section D. Applicants' arguments have been fully considered but not found persuasive.

Examiner acknowledges that the promoter used by Leinwand *et al.* is a heart specific promoter, however they are obtained from two different genes from two different species of mammals. The claims broadly encompass any 'characterizing gene [that] is different" (claim 1). Clearly genes from two different species of mammals would be considered different. Even under the standards of 35 USC 102 a specific sequence from one mammal would not anticipate a second different sequence from another mammal. As set forth in the previous office action because Leinwand *et al.* provide methods for making transgenic mice and characterize the resulting transgenic demonstrating that they meet all the limitations set forth in the claims, it is maintained that the teachings of Leinwand *et al.* anticipate the instant claims.

***Double Patenting***

a rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-27 and 32-60 stand provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-27 and 32-60 of copending Application No. 10/077,025.

Applicants acknowledge the basis of the rejection and request that the rejection be held in abeyance until the present claims have been found allowable.

Applicants request is noted however the rejection can not be held in abeyance. As noted in the previous office action, in the instant case the claims of each of the applications are duplicates of each other. No amendments to the claims in either application have been made. Therefore, the rejection is maintained. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Joseph T. Woitach

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